The challenge that remains is to prove the efficacy of therapy currently available and widely used.

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REFERENCES

1. Norris RM, Caughey DE, Mercer CJ, et al: Prognosis after myocardial infarction: Six year follow-up. Br Heart J 36:786-790, 1974

2. Battler A, Karliner JS, Higgins CB, et al: The initial chest x-ray in acute myocardial infarction—Prediction of early and late mortality and survival. Circulation 61:1004-1009, 1980

3. Borer JS, Rosing DS, Miller RH, et al: Natural history of left ventricular function during 1 year after acute myocardial infarction. Am J Cardiol 46:1-12, 1980

4. Kotter MN, Tabatznik B, Mower MM, et al: Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period. Circulation 47:959-966, 1973

5. Vismara LA, Amsterdam EA, Mason DT: Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 59:6-12, 1975

6. Schulze RA, Strauss HW, Pitt B: Sudden death in the year following myocardial infarction: Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. Am J Med 62:92-99, 1977

7. Moss AJ, DeCamilla J, Davis H: Cardiac death in the first 6 months after myocardial infarction: Potential for mortality reduction in the early posthospital period. Am J Cardiol 39:816-821, 1977

8. Taylor GJ, Humphries JO, Mellits ED, et al: Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. Circulation 62:960-970, 1980

9. Markiewicz W, Houston N, Debusk RF: Exercise testing soon after myocardial infarction. Circulation 56:26-31, 1977

10. Smith JW, Dennis CA, Gassmann A, et al: Exercise testing three weeks after myocardial infarction. Chest 75:12-16, 1979

11. Theroux P, Waters DD, Halphen C, et al: Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 301:341-345, 1979

12. Turner JD, Schwartz KM, Logic JR, et al: Detection of residual jeopardized myocardium 3 weeks after myocardial infarction by exercise testing with thallium-201 myocardial scintigraphy. Circulation 61:729-737, 1980

13. Stein RA, Walsh W, Frank F, et al: Clinical value of early exercise testing after myocardial infarction. Arch Intern Med 140: 1178-1181, 1980

14. Koppes GM, Kruyer W, Beckmann CH, et al: Response to exercise early after uncomplicated acute myocardial infarction in patients receiving no medication: Long-term follow-up. Am J Cardiol 46:764-769, 1980

It's Not Just How Low You Make It, but How You Make It Low

IN THE MAIN, acute severe hypophosphatemia induces dysfunction in organs whose tissue stores of inorganic phosphate (P_i) are already seriously depleted. One mechanism by which acute severe hypophosphatemia can induce organ dysfunction is by so severely depleting cellular stores of P_i that cellular P_i becomes determining of both the concentration and rate of regeneration of adenosine triphosphate (ATP). When severe, depletion of cytoplasmic P_i can restrict both anaerobic and aerobic *regeneration* of ATP from adenosine diphosphate (ADP) and P_i. Also, in the liver and renal cortex, depletion of P_i can increase the rate at which cytoplasmic adenosine monophosphate (AMP) is deaminated to inosine monophosphate (IMP). Because the adenine nucleotides ATP, ADP and AMP are in equilibrium in the cytoplasm of all cells, and because the deamination of AMP enhanced by cytoplasmic depletion of P_i (by deinhibiting cytoplasmic AMP deaminase) is irreversible, acute severe cytoplasmic depletion of P_i in the liver and renal cortex can induce in these tissues severe reductions in the *concentration* of total adenine nucleotides and in particular that of ATP.

As emphasized by Dr. James Knochel in his interesting and eminently useful review of hypophosphatemia elsewhere in this issue, ATP is the most important energetic currency of the cell, and one might predict that a severe reduction of either the cellular concentration or regeneration of ATP could give rise to disorders of cell function and structure. In fact, in clinical states of severe hypophosphatemia, severe reductions of P_i and ATP have been documented in the erythrocyte, leukocyte, platelet and somatic muscle, and therapeutic replenishment of depleted P_i can be attended by reestablishment of biochemical and functional integrity of these tissues. In particular, in hypophosphatemic chronic alcoholic patients and in patients rendered hypophosphatemic by excessive ingestion of antacid, severe depletion of P_i predictably occurs in somatic muscle and sometimes in the myocardium, and the depletion can cause a clinically important functional disorder that can be corrected with therapeutic replenishment of P_i.

Yet, the indications for phosphate therapy remain unclear. As pointed out by Dr. Knochel, intravenous administration of phosphate is not without risk. It has been known for many years that severe hypophosphatemia often occurs during treatment of diabetic ketoacidosis with insulin. In this setting, clear-cut biochemical and physiological abnormalities of leukocytes and erythrocytes have been shown. There is no persuasive evidence, however, that administering phosphate to prevent or correct the hypophosphatemia reduces either the morbidity or mortality of diabetic ketoacidosis. *Anabolism* has often been invoked to explain the occurrence of hypophosphatemia during (1) treatment of patients with diabetic ketoacidosis, (2) withdrawal of alcohol in alcoholic persons and (3) the initial period of feeding or hyperalimen-

tation in malnourished patients. In fact, relatively little is known of the details of such evident accumulation of tissue phosphate in any of these acutely hypophosphatemic conditions. Even when phosphate therapy is not given to patients with diabetic ketoacidosis, the severity of their hypophosphatemia characteristically moderates shortly after diabetic ketoacidosis is corrected. Thus, in patients with this disturbance, the acute severe hypophosphatemia that attends its initial treatment reflects a metabolic disorder different from that reflected by the persisting hypophosphatemia of patients with chronic alcoholism who are withdrawing from alcohol. It is important then to distinguish between the capacity of acute severe hypophosphatemia to induce metabolic and physiological disorder and the likelihood that hypophosphatemia in a given clinical setting reflects a disorder that should be treated with phosphate.

It should not be inferred that only severe hypophosphatemia induces or reflects metabolic disorders that will respond favorably to phosphate therapy. Specifically, it cannot be assumed that (1) only severe hypophosphatemia can induce, or reflect, a depletion of tissue P_i severe enough to cause a clinically important metabolic or physiologic disturbance or (2) that the pathogenetic mechanism of a hypophosphatemic metabolic disorder that can respond to phosphate therapy necessarily depends on severe depletion of cellular P_i. For example, if even moderately severe hypophosphatemia is present at the outset of diabetic ketoacidosis, the hypophosphatemia probably reflects very severe depletion of tissue stores of phosphate, and phosphate should be administered. The characteristically explosive hypophosphatemic syndrome of disturbed mentation that is often associated with paresthesias can respond dramatically to phosphate therapy, even when hypophosphatemia is not severe.

Severe intracellular depletion of phosphate with only minimal to moderate hypophosphatemia is predictably induced by the intravenous administration of certain sugars that are very rapidly phosphorylated in certain tissues. One of these sugars, fructose, is still rather widely used clinically. Sorbitol, which is converted to fructose in the liver (and presumably in the renal cortex as well), xylitol, glycerol and mannose are, like fructose, caloric substances which can induce severe intracellular depletion of P_i and substantial reductions of ATP and total adenine nucleotides in the liver and renal cortex. Fructose and xylitol have been marketed for intravenous administration and claimed to have special nutritional advantages. In this country, intravenously administered fructose and invert sugar (the 1:1 fructose/glucose product of the hydrolysis by invertase of sucrose) are used in the treatment of diabetic ketoacidosis and as a source of calories postoperatively. There would appear to be no compelling clinical indications for intravenously administered fructose, xylitol, glycerol or sorbitol. All of these sugars are potentially dangerous because their intravenous administration can induce severe tissue depletion of P_i, the above stated metabolic consequences and, in the case of fructose, severe lactic acidosis as well.[1] It is apparent that intravenous administration of these sugars might be fraught with particular risk in those clinical conditions in which severe tissue depletion of phosphate already exists.

The quintessential instance of incisive depletion of tissue phosphate is that depletion induced in patients with hereditary fructose intolerance (HFI), when these patients are exposed to fructose in even small amounts. In this instance, genetically deficient aldolase "B" in the liver, renal cortex and epithelium of the small bowel dictates these tissues' accumulation of fructose-1-phosphate in great amounts and consequent severe cellular depletion of phosphate.[2] Inadvertently, a number of patients with HFI have been severely fructose intoxicated in a hospital setting. One of these patients, a 12-year-old boy with known HFI, died as a direct and near immediate consequence of his intravenous receipt of invert sugar in the postoperative state; it was not appreciated that fructose comprises half of invert sugar. This patient had extremely severe hyperchloremic acidosis, hypophosphatemia and acute renal failure (without antecedent hypotension or evidence of renal disease).

In patients with HFI, the intravenous administration of fructose induces a dose-dependent complex dysfunction of the renal tubule with the features of Fanconi syndrome and type II "proximal" renal tubule acidosis.[3] The renal dysfunction occurs in combination with a dose-dependent hypophosphatemia and hyperuricemia, neither of which is caused by the renal dysfunction. The hyperuricemia is the consequence of degradation of preformed adenine nucleotides. By activating cytoplasmic AMP deaminase, the fructose-induced depletion of P_i enhances the irreversible deamination of AMP to IMP, a precursor of uric acid via the sequence, inosine, hypoxanthine, xanthine.[4]

Both the renal dysfunction and the hyperuricemia can be induced by fructose in amounts that cause no symptoms and induce only modest hypophosphatemia. Yet, the renal dysfunction and hyperuricemia, and the increased urinary excretion of inosine, hypoxanthine and xanthine experimentally induced by fructose, are strikingly attenuated by prior intravenous loading with phosphate.[5] In patients with HFI, Mock and his associates have recently found that an experimental relaxation of fructose restriction that did not give rise to symptoms did induce within three days persisting hyperuricemia, hyperuriocosuria and transient hypophosphatemia demonstrable only in the postprandial period.[6] One could predict that the hyperuricemia-hyperuricosuria of this circumstance could be attenuated by increased dietary intake of phosphate. It is of interest in this regard that many adult patients as well as children with HFI continually drink rather large amounts of milk. Milk provides not only nonfructose sugar but also substantial amounts of phosphate, as noted by Dr. Knochel.

Glorieux and his colleagues have shown that in children with hypophosphatemic rickets, somatic growth is enhanced and metabolic bone disease prevented or mitigated when phosphate is administered on a continuing basis in combination with vitamin D.[7] These observations provide, perhaps, the best evidence that chronic phosphate therapy can be greatly beneficial in a disease characterized by chronic, moderately severe hypophosphatemia.

One can predict the identification of disease states in which even normal concentrations of P_i in the cytoplasm will not enable (1) rates of P_i transport across the mitochondrial membrane sufficient to underwrite normal rates of regeneration of ATP or (2) normal (physiological) supression of AMP deaminase. One can envision a mitochondrial membrane disordered such that a phosphate transport mechanism has a reduced affinity or capacity for P_i. In brush border membrane vesicles prepared from the kidneys of X-linked hypophosphatemic mice, Scriver and his associates have recently reported an apparently isolated impairment of phosphate transport.[8] In the renal tubule, impaired transport of P_i by the mitochondrial membrane might be predicted to give rise to a complex derangement of energy-requiring transepithelial transport function. In this regard, it is of interest that Al-Bander and his colleagues have recently shown that phosphate loading strikingly attenuates the Fanconi-like complex dysfunction of the proximal renal tubule induced by maleic acid in dogs.[9]

One can envision a disorder of the renal tubule in which cytoplasmic P_i fails to suppress AMP deaminase. The basis of such failed suppression could be of two general kinds: either the enzyme itself is abnormal in a way that precludes its suppression by normal concentrations of cytoplasmic P_i or the renal tubule cannot maintain normal concentrations of P_i in that part (or compartment) of the cytoplasm that contains the enzyme. In view of the evidence that in rats and chickens a substantial amount of the uric acid excreted in urine is produced in the kidney,[10] the occurrence of hyperuricosuria in humans, particularly in the absence of hyperuricemia, could reflect an impairment of P_i-dampening of renal AMP deaminase. If in such a disorder the cytoplasmic concentration of P_i in the renal tubule can be increased by phosphate therapy, the severity of nephrogenic hyperuricosuria might be reduced by phosphate therapy. In fructose-loaded rats, prior loading with phosphate prevents the otherwise substantial reduction in concentrations of total adenine nucleotides in the renal cortex, but only modestly attenuates this reduction in the liver.[11] Because the activity of AMP deaminase in the renal cortex appears to reflect the same isoenzyme as that in the liver, the differential attenuating effect of phosphate loading could reflect the presumed greater access of administered phosphate to the cytoplasm of cells of the renal cortical tubules, owing to their high-affinity, high-capacity transepithelial transport process for phosphate.[11] Several lines of evidence support the proposition that hyperuricosuria is a critical determinant of the formation not only of uric acid kidney stones but also of that majority of kidney stones principally containing calcium oxalate.[12] The demonstrated effectiveness of allopurinol in reducing the severity of hyperuricosuria and the clinical frequency of nephrolithiasis[12] may depend in part on the drugs suppressing the renal production of uric acid.[10] There is some evidence that phosphate therapy is effective in reducing the clinical frequency of nephrolithiasis. It will be of considerable interest to determine whether phosphate therapy is most effective in those patients in whom it reduces the severity of hyperuricosuria and inosinuria.

It seems likely that in the next few years many clinically important dysphosphatotic conditions will be described. It also seems likely that a num-

ber of such conditions will not be characterized by hypophosphatemia. There is reason to be hopeful that careful clinical and biochemical definitions of these anticipated conditions will enable many of those affected to be successfully treated.

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REFERENCES

1. Woods HF, Alberti KGMM: Dangers of intravenous fructose. Lancet 2:1354-1357, Dec 23, 1972

2. Froesch ER: Essential fructosuria and hereditary fructose intolerance, *In* Stanbury JB, Wyngaarden JB, Fredrickson DS (Eds): The Metabolic Basis of Inherited Disease, 3rd Ed. New York, McGraw-Hill Book Co, 1972, pp 131-148

3. Morris RC Jr: An experimental renal acidification defect in patients with hereditary fructose intolerance—II. Its distinction from classic renal tubular acidosis: Its resemblance to the renal acidification defect associated with the Fanconi syndrome of children with cystinosis. J Clin Invest 47:1648-1663, 1968

4. Maenpaa PH, Ravio KO, Kekomaki MP: Liver adenine nucleotides: Fructose-induced depletion of its effect on protein synthesis. Science 161:1253-1254, 1968

5. Morris RC, Brewer ED, Brater C: Evidence of a severe phosphate-depletion-dependent disturbance of cellular metabolism in patients with hereditary fructose intolerance (HFI), abstracted. Clin Res 28:566a, 1980

6. Mock DM, Tsai H, Perman JA, et al: Chronic fructose intoxication in apparently asymptomatic patients with hereditary fructose intolerance (HFI), abstracted. Clin Res, 1981 (In Press)

7. Glorieux FH, Scriver CR, Reade TM, et al: Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. N Engl J Med 287:481-487, 1972

8. Tenenhouse HS, Scriver CR, McInnes RR, et al: Renal handling of phosphate *in vivo* and *in vitro* by the X-linked hypophosphatemic male mouse: Evidence for a defect in the brush border membrane. Kidney Intl 14:236-244, 1978

9. Al-Bander H, Mock DM, Paukert T, et al: Phosphate loading attenuates the severity of the renal tubular disorder induced by maleic acid (MA) in the dog, abstracted. Clin Res, 1981 (In Press)

10. Chin TY, Cacini W, Zmuda MJ, et al: Quantification of renal uric acid synthesis in the rat. Am J Physiol 238:F481-F487, 1980

11. Morris RC Jr, Nigon K, Reed EB: Evidence that the severity of depletion of inorganic phosphate determines the severity of the disturbance of adenine nucleotide metabolism in the liver and renal cortex of the fructose-loaded rat. J Clin Inves 61:209-220, 1978

12. Coe FL: Nephrolithiasis—Pathogenesis and Treatment. Chicago, Year Book Medical Publishers, 1978, pp 1-235

Physicians' Fees—Not Too Bad a Record

A RECENT COMMUNICATION in the *Journal of the American Medical Association* by G. L. Glandon and J. R. Werner[1] reviews physicians' practice experience in the decade of the 1970's. Data were collected by the AMA Center for Health Services Research and Development in 1970 and 1980, with particular attention to average incomes, expenses and fees. These are considered in relation to the real gross national product, which declined in the 1970's, and the cost of living, which doubled.

While physicians' net incomes are projected to have increased from $41,800 in 1970 to $80,000 by the end of 1980, their real income in uninflated dollars changed little if at all. Practice expenses rose from $24,300 in 1970 to a projected $54,500 in 1980. As gross income increased practice expenses rose commensurately.

During the 1970's physicians' fees were the subject of considerable attention and criticism by government and others. However, the facts appear to show that the real income of physicians did not rise and in fact remained essentially unchanged. This is not too bad a record.

—MSMW

REFERENCE

1. Glandon GL, Werner JL: Physicians' practice experience during the decade of the 1970s (Special Communication). JAMA 244:2514-2518, Dec. 5, 1980